Initiation, Propagation, and Termination of Epileptiform Activity in Rodent Neocortex *In Vitro* Involve Distinct Mechanisms

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Goals of the Paper

- Support the hypothesis that epileptiform activity in the rat cortex has three distinct stages and each is governed by different mechanisms (following from a perturbation analysis study done by Ermentrout and Pinto)
- Examine excitation and inhibition of system in each stage by use of receptor antagonists
- Develop a better overall model of epileptiform activity (future medical benefits)

Key Words

- Epileptiform-Resembling epilepsy or any of its symptoms (brain function)
- Picrotoxin (PTX)-GABA receptor antagonist which elicits epileptiform activity (disinhibitor)
- 6,7-dinitroquinoxaline-2,3-diome (DNQX)-Blocks AMPA receptors (inhibitor)

Epileptiform Activity: 3 Stages

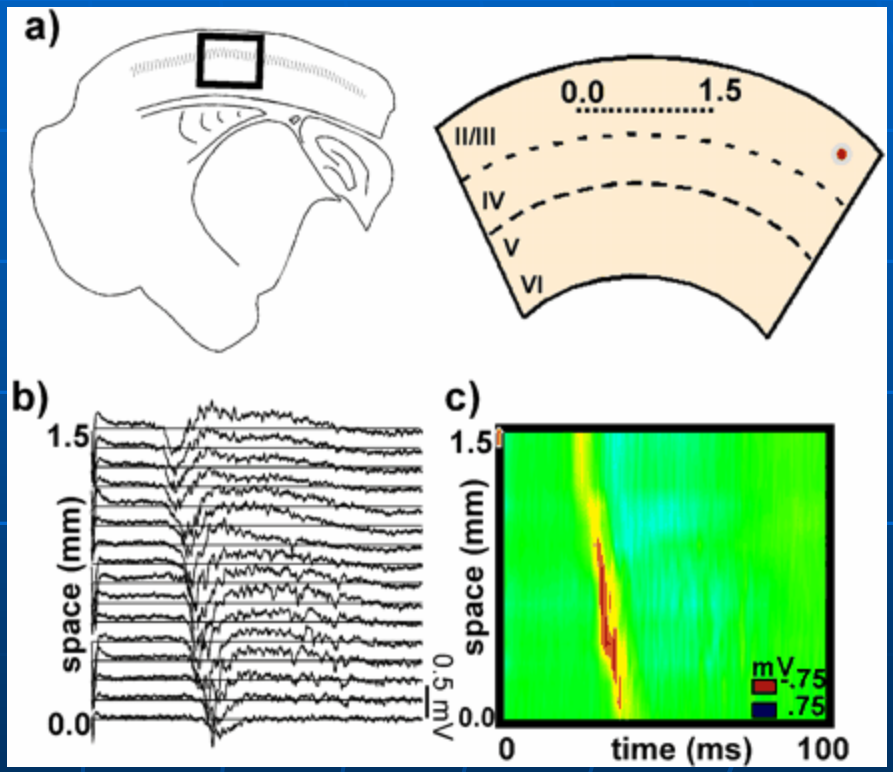
- **Initiation**-Transition from sparse, asynchronous, local activity to dense synchronous and outwardly spreading activity in the somatosensory cortex
- **Propagation**-Synchronous pulse from one neuron population to the next
- **Termination**-The failure of Propagation

Methods

- 140 slices of the somatosensory cortexes of 96 rats were utilized *in vitro* to test the hypothesis
- All drugs used were titrated into a bathing solution of the slices

Methods (cont.)

- 16 microwires spanning 1.5mm in the rat cortex were used to test brain activity
- Epileptiform activity was evoked by a combination of PTX titration and a stimulating electrode

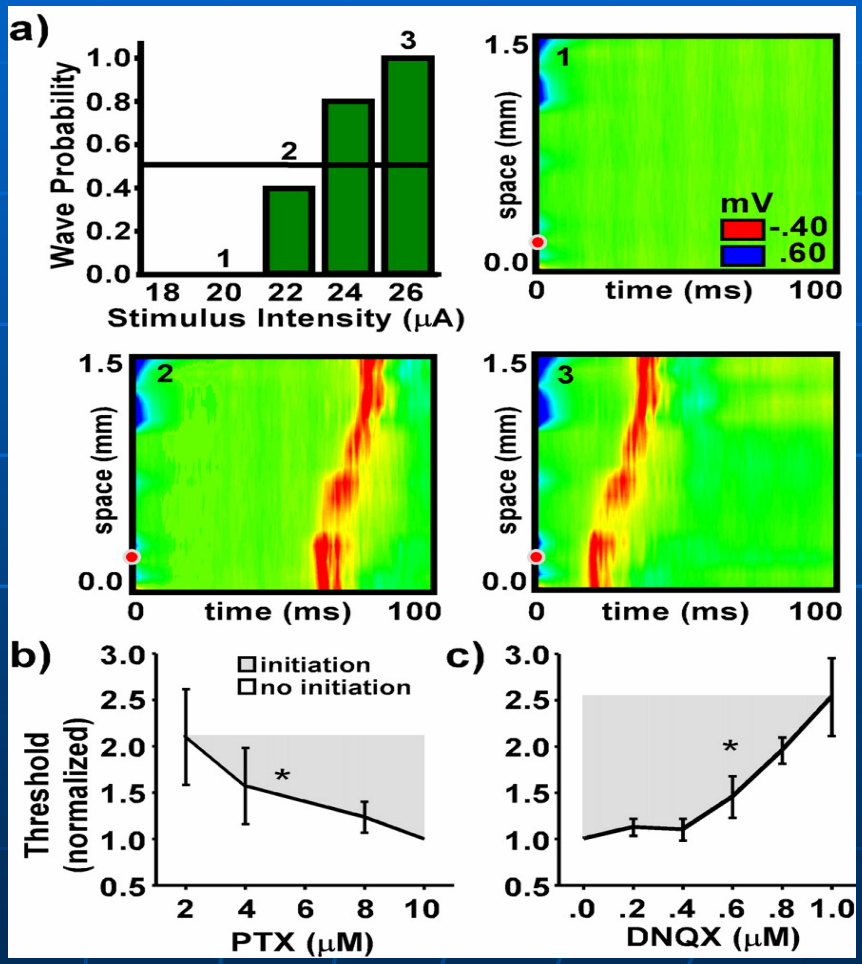


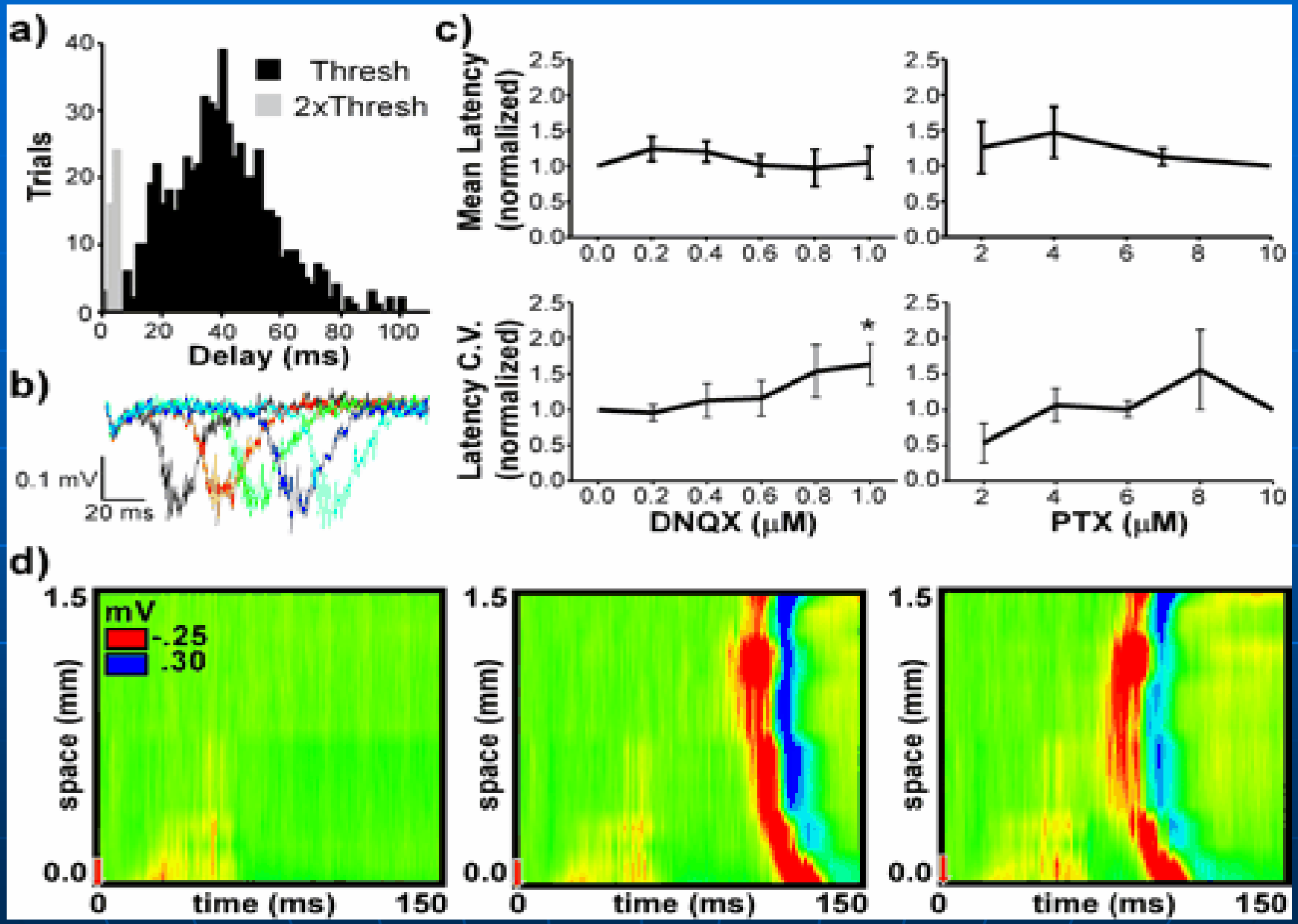
Results: Initiation

- They discovered that there was an all-or-none response with a sharp threshold value when cortical slices were stimulated
- Threshold was defined as the lowest intensity at which one-half of the slices induced waves

Initiation (cont.)

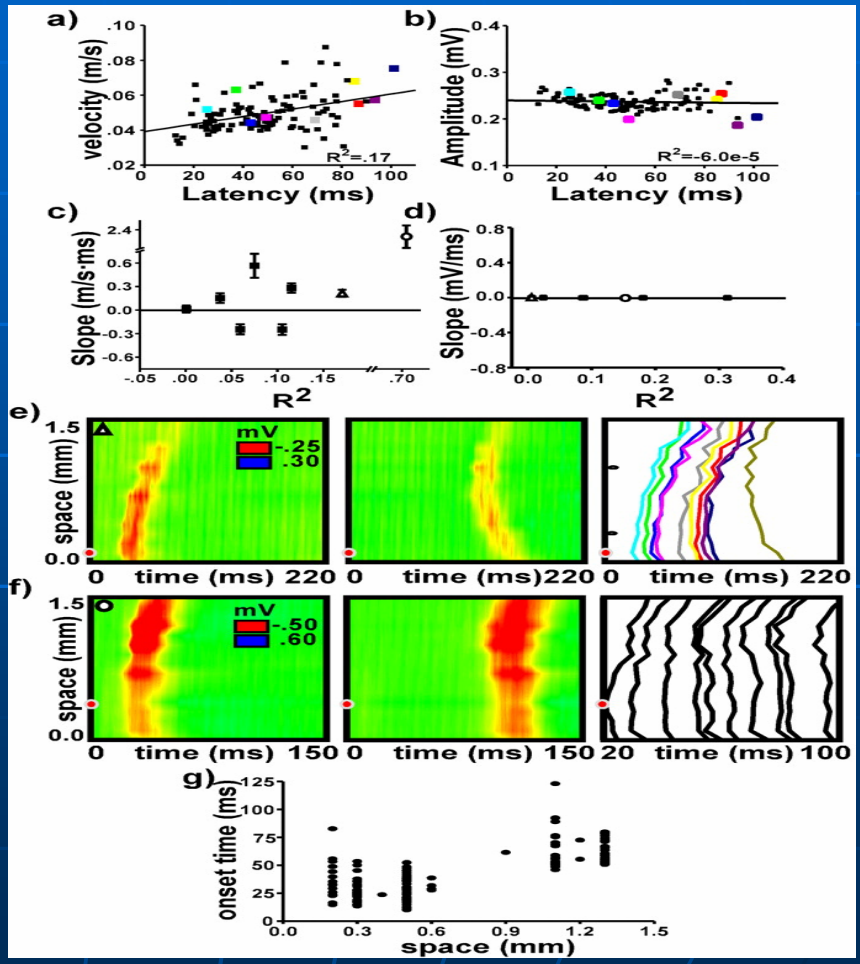
- Waves induced at near-threshold intensities often had a delay before initiating their waves
- To reach threshold, there needed to be at least 2-3 μM of PTX present
- With increased amount of PTX, the threshold lowered, and DNQX caused the threshold to increase
- Thus, both inhibitory and excitatory factors are influential

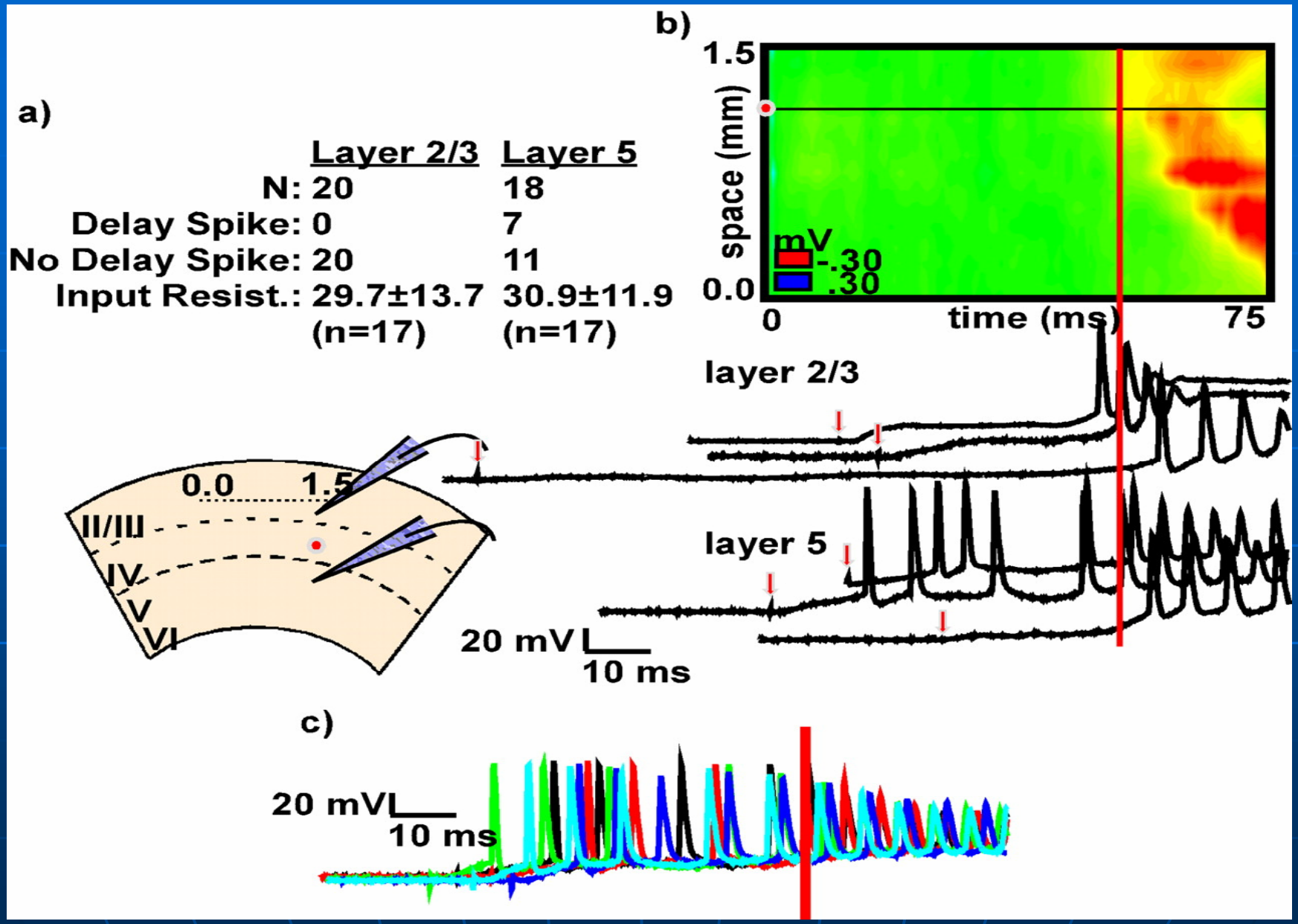



a)
Thresh
2xThresh
Trials
Delay (ms)
b)
0.1 mV
20 ms
c)
Mean Latency (normalized)
Latency C.V. (normalized)
DNQX (μM)
PTX (μM)
d)
mV
-.25
.30
space (mm)
time (ms)

A Look at Two Phases: Initiation and Propagation

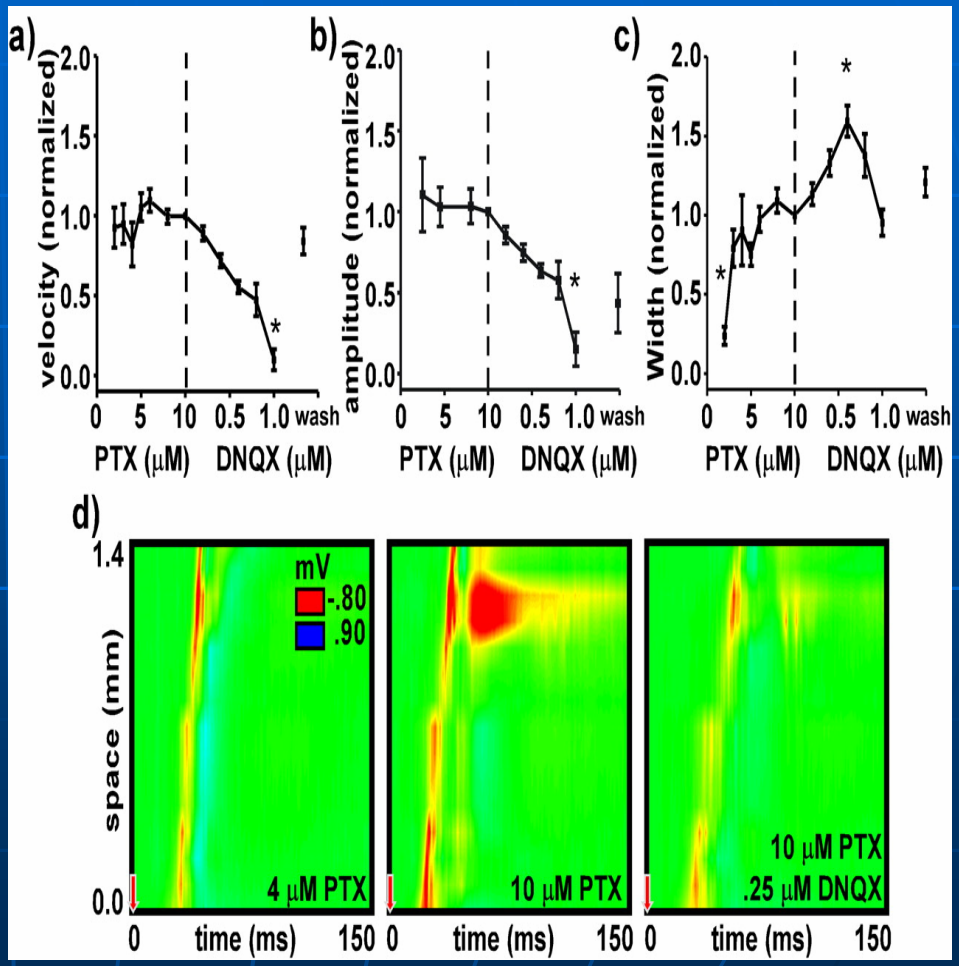
- Brain wave amplitude was independent of the delay of the waves with near-threshold stimuli
- However, wave velocity increased slightly for longer delays




a)
Layer 2/3 Layer 5
N: 20 18
Delay Spike: 0 7
No Delay Spike: 20 11
Input Resist.: 29.7±13.7 30.9±11.9
(n=17) (n=17)
b)
1.5
space (mm)
0.0
mV
-.30
.30
0
time (ms)
75
layer 2/3
layer 5
0.0
1.5
II/III
IV
V
VI
20 mV
10 ms
c)
20 mV
10 ms

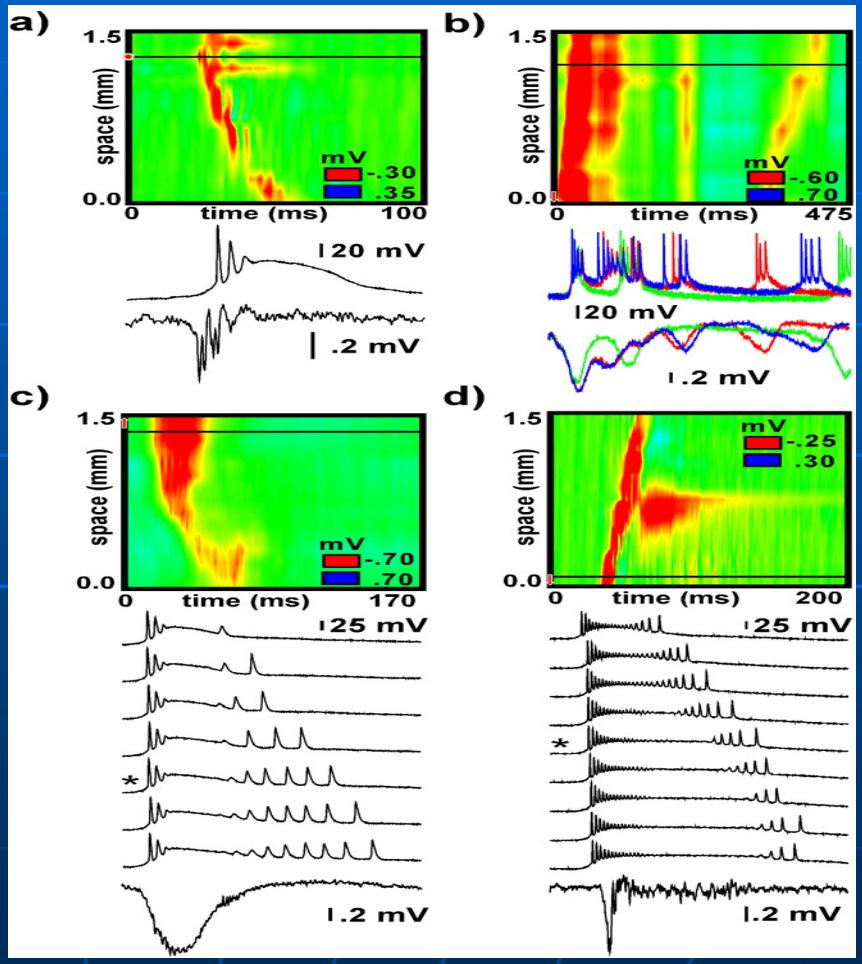
Propagation

- Involved titration of PTX onto the cortical slices, followed by DNQX until the end of propagation
- As PTX increased (inhibitory factor), velocity and amplitude of the wave was not affected
- As DNQX increased (excitatory factor), a decrease in amplitude and velocity was observed



Termination

- This occurs at specific points in the rat cortex
- Termination of the initial wave coincides with an extended depolarization of the individual neurons
- Often, secondary activity was present after the first wave terminated (high variability)
- Cortical slices were also stimulated repeatedly, and it was observed that “recovery spikes” were present



Conclusions

- Overall, results supported the hypothesis each stage has a distinct mechanism
- It was determined that the initiation stage depended on both synaptic excitation and inhibition, and was a process that occurred in cortical layer 5 of the rat cortex
- Propagation depended on excitation but not inhibition
- Termination was characterized by an extended depolarization of neurons

New Findings

1. Sub-threshold shift of the initiation point from the stimulus
2. The actions of cortical layer 5 as opposed to those of layer 2/3 before initiation of the wave
3. Variability of activity after the first wave terminates

Thanks for your time.

Questions??